IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Su Chen

Title: OXYGEN-18 LABELED ORGANIC ACIDS AND USE IN DIAGNOSING METABOLIC DISORDERS

Appl. No.: 10/696,051

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Examiner: Weisz, D.G.

Art Unit: 1777

Conf. No: 5893

PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Commissioner for Patents
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Sir:

In accordance with the **Pre-Appeal Brief Conference Pilot Program**, announced July 11, 2005, this Pre-Appeal Brief Request is being filed together with a Notice of Appeal. Applicant requests reconsideration of the present application in view of the reasons that follow.

Rejection of claims under 35 USC § 112, second paragraph

Claims 1, 3-4, 6-13, 15-17, 30-32, 34-41, and 43-61 stand rejected as allegedly indefinite. In maintaining this rejection, the Examiner has failed to identify any claim element or specific wording that is alleged to be indefinite. Instead, the Examiner makes several statements regarding the claim interpretation and concludes that the claims recite convention usage of a labeled internal standard for quantifying an analyte. Final Office Action at page 2, Item 4. To the extent that the Examiner questions whether the sample contains unlabeled and labeled organic acids, Applicant submits that the claim language clearly states that labeled organic acids are added to a sample suspected of containing an unlabeled organic acid. In the Examiner's remarks (Final Office Action at page 5, Item 9), the Examiner alleges that step (c), presumably of claim 1, is unclear, but gives no specific reasoning, rationale, or interpretation to support this allegation. In response,

Applicant submits that, as acknowledged by the Examiner, the ^{18}O-labeled organic acid is being used as an internal standard which is used to account for any loss of material in the processing and detection steps, and to calibrate the detection methodology to a known amount of analyte in order to provide a basis for quantifying the analyte of interest. This use of an internal standard is routine in the art and is clearly specified in the claims. In sum, the Examiner has not identified a specific claim limitation that is indefinite, thereby rendering this rejection deficient. Applicant has attempted to address certain statements made by the Examiner and respectfully submits that the claims are definite, as written. Accordingly, this rejection is traversed and should be withdrawn.

Claims 7-8, 12-13, 31-32, and 40-41 stand rejected as allegedly indefinite. In maintaining this rejection, the Examiner alleges that terms "enrichment" and "chemical modification" are indefinite because the a specific method of enrichment and that there are many chemical processes that may result in a chemical modification. Final Office Action at page 2, Item 5, and paragraph bridging pages 5-6. The Examiner appears to be equating overbreadth with indefiniteness which has been held to be an improper basis of support for this type of rejection. In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971); MPEP § 2173.04. Contrary to the Examiner's allegation, there is no requirement under 35 U.S.C. § 112, second paragraph, that the claims recite any particular means for enrichment or chemical modification. As previously noted by Applicant, and not refuted by the Examiner, the Specification provides clear definitions and guidance on these terms. See, Specification at [0060]-[0061]. Other than the alleged overbreadth, the Examiner has not put forth any argument that these terms themselves are indefinite or otherwise unclear. Accordingly, this rejection is traversed and should be withdrawn.

Rejection of claims under 35 USC § 103

All examined claims stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Peterson et al. (J. Lipid Res., 29: 94-101, 1988; "Peterson") in view of Nguyen et al. (US 2005/0070023; "Nguyen") either alone or in further combination with Pang (HKMJ 2: 264-273, 1996). The Examiner reads Peterson as disclosing the synthesis and mass spectrometric (MS) detection of [^{18}O]-labeled glycolic acid (a hydroxyl mono-acid). The Examiner acknowledges that Peterson does not disclose using this [^{18}O]-labeled acid as an internal standard but turns to Nguyen, alleging that Nguyen discloses the use of organic acids labeled with stable isotopes as internal standards for MS analysis. Finally, the Examiner relies on Pang to demonstrate that prior

art measured organic acid levels in urine to diagnose metabolic disorders. Applicant respectfully traverses this rejection.

Independent claims 1, 9, 30, and 37 each require that the sample under analysis is a biological sample. The requirement for the use of biological samples is one basis for non-obviousness over the cited prior art.

As an initial matter, Applicant takes issue with the Examiner's interpretation of the claim requirement for a "biological sample." The Examiner alleges that this term is entitled to its broadest reasonable interpretation and that glycolic acid itself is a biological substance. Final Office Action at page 6, first paragraph. This leads the Examiner to conclude that the sample of Peterson, which contains glycolic acid, is a biological sample for the purposes of this rejection. Final Office Action at page 3, third paragraph. This is clearly a specious and unreasonable interpretation which is inconsistent with the definition provided in the Specification. The Specification states:

> By "sample" is meant a sample obtained from a biological source, e.g., an organism, cell culture, tissue sample, and the like.
>
> Specification at [0009] (emphasis added).

As is evident from the discussion below, Peterson does not provide a sample "obtained from a biological source" and the mere addition of glycolic acid to a solvent solution does not render the sample "biological" for the purposes of the present invention. Peterson discloses that glycolic acid is important in photorespiration and therefore may be obtained from a biological source, but Peterson's sample is purely synthetic, not biological. This distinction is important because, as discussed below, biological samples are complex mixtures containing a variety of other oxygen-containing compounds which may have the potential to exchange or otherwise displace the [^{18}O] label from the labeled organic acid.

The Examiner relies on Peterson as the only reference that actually synthesizes and detects by MS an [^{18}O]-labeled organic acid. Peterson prepares [^{18}O]-glycolic acid by heating choloroacetic acid in the presence of [^{18}O]-H_2O. Next, Peterson derivatizes the [^{18}O]-glycolic acid using bis(trimethylsilyl) trifluoroacetamide (BSTFA), neutralizes the derivatized sample, and detects the derivatized [^{18}O]-glycolic acid by MS. Peterson et al. at pp. 95-96.

There is nothing in Peterson that teaches or suggests that [^{18}O]-glycolic acid is suitable for use as an internal standard with a biological sample. As noted above, Peterson creates [^{18}O]-glycolic acid with a substitution reaction in which one or more of the carboxylic acid and the alcoholic [^{16}O] atoms in glycolic acid is substituted with [^{18}O] from the solvent, [^{18}O]-H_2O. Peterson's [^{18}O]-glycolic acid is then analyzed in a sample devoid of any other oxygen-containing compounds, such as proteins or other organic acids, that may provide an opportunity to re-exchange the [^{18}O] for an [^{16}O]. Because generation of the [^{18}O]-glycolic acid occurs by a mere replacement reaction in the presence of [^{18}O]-H_2O, Peterson provides no reasonable expectation that the [^{18}O] atoms from the [^{18}O]-glycolic acid, once labeled, would not re-exchange with other carboxylic acid and/or alcoholic oxygen atoms in the plethora of unlabeled biological molecules (e.g., proteins) and/or other organic acids found in a complex biological samples such as urine.

Furthermore, Nguyen (relied upon by the Examiner) demonstrates that this potential problem was known in the art and teaches away from using an isotopic label such as [^{18}O] under circumstances when the labeled analyte is generated by a simple isotope exchange reaction such as that demonstrated by Peterson. In discussing the use of isotopic labels, Nguyen states:

> The ideal [internal standard], however, must not contain any labeled isotope that can be exchanged for the unlabeled isotope under particular sample preparation conditions.
>
> Nguyen et al. at [0005].

Nguyen goes on to characterize suitable stable isotopes as follows:

> Most often the synthesis of stable isotope internal standards is not simply an isotope exchange reaction. Easily exchangeable atoms are usually avoided due to possible re-exchange during sample preparation steps.
>
> Nguyen et al. at [0006]. Emphasis added.

Thus, the use of the [^{18}O]-glycolic acid of Peterson for an internal standard, as alleged by the Examiner, is exactly contrary to the admonitions of Nguyen. As discussed above, the [^{18}O]-glycolic acid of Peterson is formed by a simple exchange reaction; exactly the type that could result in re-exchange during sample preparation. The Examiner has provided no reasoning as to why the skilled artisan would ignore Nguyen's express teaching away and have any reasonable expectation of success in the use of the [^{18}O]-labeled organic acids as internal standards.

In attempting to address the teaching away provided by Nguyen, the Examiner relies on Nguyen's statement that [^{18}O] is a commonly-used stable isotope for labeling internal standards. Final Office Action at page 6, second paragraph. Applicant does not disagree that [^{18}O] has been previously used for labeling molecules of interest. However, Applicant notes that there are a variety of oxygen-containing chemical moieties into which [^{18}O] may be incorporated (e.g., alcohol, ester, ether, heterocyclic ring structures, etc.). But, not all of these chemical moieties have freely-exchangeable oxygen atoms. Based on the teachings of Nguyen, the artisan would not be motivated to use an [^{18}O]-labeled compound having the [^{18}O] atom present at an exchangeable site.

Thus, the affirmative teachings of Nguyen do not remedy the deficiencies of Peterson, nor do they negate Nguyen's general teaching away from the use of free-substituted isotopic labels, which include [^{18}O] in the labeling reaction of Peterson. Although Nguyen generally discloses that internal standards may be isotopically labeled with any number of stable isotopes (Nguyen et al. at [0005]), Nguyen synthesizes a deuterium-labeled organic acid. Nguyen et al. at [0027]-[0032]. Thus, Nguyen does nothing to demonstrate that [^{18}O]-labeled organic acids may be used as internal standards for mass spectrometry.

Pang also fails to remedy the deficiency in the *prima facie* case of obviousness based on Peterson and Nguyen. Pang merely discloses that the levels of organic acids may be measured in urine as an indicator of metabolic disease. However, nothing in Pang is related to the MS detection of organic acids, let alone the use of [^{18}O]-labeled organic acids in biological samples.

For the foregoing reasons, Applicant respectfully submits that all obviousness rejections based on the combination of Peterson and Nguyen are traversed and should be withdrawn.

Respectfully submitted,

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